REMARKS

Status of the Claims

Claims 1-29 were pending. Claims 1-29 were rejected. Claims 1, 9, 18, 19, 23, 24, 25, and 29 have been amended. Claims 30 and 31 have been added. Claim 4 has been canceled without prejudice. Support for the amendment to claim 5 can be found throughout the application, but specifically on page 9, lines 1-3. Support for the amendment to claim 9 can be found throughout the application, but specifically on page 21, line 13 to page 22, line 9. Support for new claims 30 and 31 can be found throughout the application. Upon entry of this amendment and these remarks claims 1-3 and 5-31 will be pending. No new matter has been added.

Objections

Claims 1-29 stand objected for allegedly not using proper English grammar. Claims 1, 9, 18, 18, 23, 24, 25, and 29 have been amended rendering this objection moot.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 4, 18-22 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully disagree.

Claims 4 has been canceled and claim 18 has been amended rendering this rejection moot.

Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-29 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent 5,593,972 (hereinafter, the "'972 patent"). The Examiner alleges that Weiner *et al.* discusses methods of prophylactic and therapeutic immunization of an

individual against pathogen infections, diseases associated with hyperproliferative cells and autoimmune diseases. The Examiner also suggests that Weiner *et al.* discusses a method comprising administering a nucleic acid molecule that comprises a nucleic acid encoding the protein wherein the nucleic acid is operably linked to a promoter and a polyA signal and wherein the promoter enables the expression of the protein in the cells. Applicants respectfully disagree.

The standard for anticipation under 35 U.S.C. § 102(b) is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

The amendments of the claims renders this rejection moot. The '972 patent does not discuss the methods claimed in the present Application. The '972 patent fails to disclose a method of delivering a protein to a macrophage cell or cells of macrophage derived lineage using a macrophage specific promoter. Furthermore, the amendment of claim 9 that added the step of selecting a lymphnode before delivering a protein to that lymphnode is not discussed in the '972 patent.

Thus, the '972 patent does not disclose each limitation of the claims and therefore cannot anticipate the present invention. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Claims 1-7, 9-15, 17, 18, and 20-23 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Song *et al.* (*PNAS*, **94**:1943-1948, 1997). The Office alleges that Song *et al.* discusses a method of gene transfer, protein expression and antigen presentation after intramuscular administration of retroviral vectors to mice. Applicants respectfully disagree.

Song *et al.* discusses infecting mice using Moloney murine leukemia virus-based retroviral vectors. The authors use the vector to produce high titer viruses, (>1 X 10^7 colony-forming units), which are then used to infect the animals.. Although, not explicitly disclosed in the Song reference the Moloney murine leukemia virus contains a linear RNA genome that is surrounded by proteins that form the capsid. After infection,

the virus, under normal conditions, integrates into the host cell. This is in contrast to what is described and claimed in the present application.

The amendments of the claims renders this rejection moot. The present application discloses methods of using DNA molecules, not RNA retroviral particles that are discussed in the Song reference. The Song reference does not disclose infecting an animal using a DNA molecule.

Thus, the Song reference does not disclose each limitation of the claims and therefore cannot anticipate the present invention. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Claims 1-26 and 29 stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 5,888,767, hereinafter the "'767 patent." The Office alleges that the '767 patent discusses, "a method of conditionally expressing a gene of interest in a cell using a replicating viral vector and methods of prophylactic and therapeutic treatments." (Office Action, page 5) The Office further alleges that the vectors comprise a promoter driving the expression of the gene of interest and operably linked to a polyA signal and that the patent discloses and discusses the types of genes that can be expressed using the vectors. Applicants respectfully disagree.

The '767 patent discusses an invention providing a conditionally replicating viral vector. (Abstract, line 1). The '767 patent defines a conditionally replicating viral vector as "a virus (which preferably is the same type of virus as the infection being treated) that replicates only upon complementation with a wild-type strain of virus or when wild-type virus infects cells containing conditionally replicating vector genome," (Col. 10, lines 9-13).

The amendments of the claims renders this rejection moot. The '767 patent does not discuss administering DNA using a macrophage specific promoter. Additionally, the '767 patent does not discuss selecting a lymphnode as is disclosed in claim 9.

Thus, the '767 patent does not disclose each limitation of the claims and therefore cannot anticipate the present invention. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 25-28 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the '767 patent in view of U.S. Patent 6,084,073, hereinafter the "'073 patent", or WO 92/13559 and Van Oijen *et al.* (Journal of Drug Targeting 5:75-91, 1998). The Office alleges that the '767 patent discusses a method of conditionally expressing a gene of interest in a cell using a replicating viral vector and methods of prophylactic and therapeutic treatments. The Office also alleges that the '073 patent discusses DNA sequences encoding ricin toxins and that WO 92/13559 discusses expressing vectors that express CD4-gamma1 chimeric heavy chain homodimers and heterodimers. The Office suggests that at the time of the present invention, it would have allegedly been obvious to the art-skilled to express ricin A or diphtheria toxin or any other toxin by modifying the vectors of the '767 patent. Applicants respectfully disagree.

As is clear from MPEP §2143, in order to provide a *prima facie* case of obviousness, the Examiner must first establish motivation to combine or modify the references.

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP §2143. The Examiner cannot rely upon a reasonable expectation of success alone to establish motivation. Such reliance is improper.

Claim 25 reads in part, "A method of eliminating cells in a lymphnode of an individual..." Claims 26-28 depend upon claim 25.

As discussed above, the '767 patent does not discuss the methods of delivering a protein to a macrophage cell or a cell of macrophage derived lineage comprising the step of administering a DNA molecule using a macrophage specific promoter. Additionally, the '767 patent does not discuss methods to eliminate a lymphnode.

Thus, even if you did combine the '767 patent with the '073 patent or WO 92/13559 and Van Oijen *et al.* you do not produce the claimed invention. The combination of the above references does not discuss methods for eliminating lymphnodes. There is no suggestion in the '767 patent or the other references cited for methods to eliminate a lymphnode. Therefore, even if a person of ordinary skill in the art were motivated to combine the references, which that person is not, the art-skilled would not be in possession of the methods that are disclosed in claims 25-28.

Therefore, there is no *prima facie* case of obviousness because there is no motivation to combine the references because none of the references suggest the combination or refer to the other references explicitly or implicitly and even if the combination were made the combination does not produce the Applicants invention.

Accordingly, Applicants respectfully request the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

Claims are in condition for allowance. An indication of allowability is therefore earnestly solicited. Applicant invites the Examiner to contact the undersigned at (215) 665-6928 to clarify any unresolved issues raised by this response.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

Please cancel claim 4 without prejudice.

Please amend claims 1, 5, 9, 18, 19, 23, 24, 25, and 29 and add new claim 30 as follows:

1. **(Amended)** A method of delivering a protein to a macrophage cell or a cell of macrophage derived lineage of an individual comprising the steps of:

administering to said individual at a site on said individual's body, a DNA molecule comprising a nucleotide sequence that encodes said protein, wherein said DNA molecule is operably linked to a macrophage specific promoter and a polyadenylation signal that are functional in a macrophage cell and/or a cell of macrophage derived lineage, wherein said DNA molecule is taken up by a macrophage cell and/or a cell of macrophage derived lineage where said nucleotide sequence is expressed to produce said protein in said macrophage cell and/or said cell of macrophage derived lineage.

5. **(Amended)** The method of claim 1 wherein said macrophage specific promoter is selected from the group consisting of: [an actin promoter, a CD11 promoter, a CD13 promoter, an MHC-I promoter, an MHC-II promoter, a CD25 promoter, a CD80 promoter, a CD86 promoter,] a catalase promoter, a CD156 promoter, an M-CSFR promoter, a p73 promoter, an FcγRI promoter[, a CMV promoter, an actin promoter, an SV40 promoter and a Malony virus promoter].

9. **(Amended)** A method of delivering a protein to a lymphnode of an individual comprising the steps of:

a) identifying said lymphnode that is to have protein delivered to;

b) [a)] locating a site on said individual's body that is proximal to said lymphnode;

c) [b)] administering to said individual at said site, a DNA molecule comprising a nucleotide sequence that encodes said protein, wherein said DNA molecule is operably

linked to a promoter and a polyadenylation signal that are functional in a macrophage cell and/or a cell of macrophage derived lineage,

wherein said DNA molecule is taken up by a macrophage cell and/or a cell of macrophage derived lineage where said nucleotide sequence is expressed to produce said protein in said macrophage cell and/or said cell of macrophage derived lineage, and

said macrophage cell and/or said cell of macrophage derived lineage drains to said lymphnode, and delivers said protein in said lymphnode.

18. **(Amended)** A method of inducing an immune response against an immunogen in an individual comprising the step of:

administering to said individual at a site on said individual's body, a DNA molecule comprising a nucleotide sequence that encodes said immunogen operably linked to a macrophage specific promoter and a polyadenylation signal that are functional in macrophage cells and/or cells of macrophage derived lineages,

wherein said DNA molecule is taken up by a macrophage cell and/or a cell of macrophage derived lineage where said nucleotide sequence is expressed to produce said immunogen in said macrophage cell and/or said cell of macrophage derived lineage and an immune response mediated by said macrophage is generated against said immunogen.

19. **(Amended)** The method of claim 18 wherein said DNA molecule further comprises

a nucleotide sequence that encodes an immunomodulating protein, wherein said DNA molecule is operably linked to a promoter and a polyadenylation signal that are functional in macrophage cells and/or cells of macrophage derived lineages, and/or

a second DNA molecule is additionally administered to said site on said individual's body, said second DNA molecule comprising a nucleotide sequence that encodes an immunomodulating protein, wherein said second DNA molecule is operably linked to a promoter that is functional in macrophage cells and/or cells of macrophage derived lineages and a polyadenylation signal that is functional in macrophage cells and/or cells of macrophage derived lineages.

23. **(Amended)** A method of modulating an individual's immune system comprising the step of:

administering to said individual at a site on said individual's body, a DNA molecule comprising a nucleotide sequence that encodes an immunomodulating protein, wherein said DNA molecule is operably linked to a macrophage specific promoter and a polyadenylation signal that are functional in a macrophage cell and/or a cell of macrophage derived lineage,

wherein said DNA molecule is taken up by a macrophage cell and/or a cell of macrophage derived lineage where said nucleotide sequence is expressed to produce said immunomodulating protein modulates said individual's immune system.

24. **(Amended)** The method of claim 23 wherein said DNA molecule further comprises

a nucleotide sequence that encodes an immunomodulating protein, wherein said DNA molecule is operably linked to a promoter and a polyadenylation signal that are functional in macrophage cells and/or cells of macrophage derived lineages and/or

a second DNA molecule is additionally administered to said site on said individual's body, said second DNA molecule comprising a nucleotide sequence that encodes an immunomodulating protein, wherein said second DNA molecule is operably linked to a promoter that is functional in macrophage cells and/or cells of macrophage derived lineages and a polyadenylation signal that is functional in macrophage cells and/or cells of macrophage derived lineages.

25. **(Amended)** A method of eliminating cells in a lymphnode of an individual comprising the step of:

administering to said individual at a site on said individual's body, a DNA molecule comprising a nucleotide sequence that encodes a cytotoxic protein, wherein said DNA molecule is operably linked to a promoter and a polyadenylation signal that are functional in a macrophage cell and/or a cell of macrophage derived lineage,

wherein said DNA molecule is taken up by a macrophage cells and/or a cells of macrophage derived lineage where said nucleotide sequence is expressed to produce said protein in said macrophage cells and/or said cells of macrophage derived lineage,

said macrophage cell and/or a cell of macrophage derived lineage secretes or releases said cytotoxic protein in said [lymph node] lymphnode eliminating cells in said lymphnode.

29. **(Amended)** A method of delivering a desired protein to an individual comprising the step of:

administering to said individual at a site on said individual's body, a DNA molecule comprising a nucleotide sequence that encodes said desired protein, wherein said DNA molecule is operably linked to a macrophage specific promoter and a polyadenylation signal that are functional in a macrophage cell and/or a cell of macrophage derived lineage,

wherein said DNA molecule is taken up by a macrophage cells and/or a cells of macrophage derived lineage where said nucleotide sequence is expressed to produce said desired protein in said macrophage cells and/or said cells of macrophage derived lineage.

30. **(New)** The method of claim 25 wherein said promoter is a macrophage specific promoter.

31. **(New)** The method of claim 25 wherein said DNA molecule is a plasmid.

In the Specification:

Please insert the following section heading and paragraph on page 1 before the first paragraph:

Cross reference to related applications

The present application is the national phase of PCT application PCT/US/99/13267, filed June 11, 1999, which claims priority to the U.S. provisional application Serial No: 60/088,980, filed June 11, 1998.

Please insert the following abstract:

Abstract

Methods of delivering a protein to a macrophage cell and/or a cell of macrophage derived lineage of an individual are disclosed. The method comprises the step of administering to the individual at a site on the individual's body, a DNA molecule that comprises a nucleotide sequence that encodes the protein linked to a promoter that is functional in a macrophage cell and/or a cell of macrophage derived lineage and a polyadenylation signal that is functional in a macrophage cell and/or a cell of macrophage derived lineage. Methods of delivering proteins to lymphnodes of an individual are also disclosed. Methods of inducing an immune response against an immunogen in an individual are disclosed. Methods of modulating an individual's immune system are also disclosed.